UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,117	11/18/2003	Jing Li	006539.00051	6377

22907 7590 09/12/2008

BANNER & WITCOFF, LTD.
1100 13th STREET, N.W.
SUITE 1200
WASHINGTON, DC 20005-4051

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
09/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,117	LI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 135-151* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, and 135-151* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, and 135-151 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 06/08/2008.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Priority

1. This instant application claims priority to provisional applications 60/427,202 (filed 11/19/2002) and 60/434,434 (filed 12-19-2002). However, the subject matter of the examined claims (claims 1-3, methods using SPHK1 gene copy number) was not disclosed in the '202 provisional application, thus the claims do not have priority to the '202 provisional application. The subject matter of the examined claims is disclosed in the '434 provisional application, thus the claims have priority to the 60/434,434 provisional application (filed 12-19-2002).

Maintained Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 135-138, 145, and 147-151 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A screening method comprising determining sphingosine kinase 1 (SPHK1) human gene copy number, wherein said sphingosine kinase 1 (SPHK1) human gene encodes an mRNA comprising SEQ ID NO: 3, in a test sample, and comparing the test sample copy number to data for a control gene copy number obtained from a control sample of the same tissue type as the test sample,

does not reasonably provide enablement for a method comprising analysis of the broadly claimed 'sphingosine kinase 1 (SPHK1) human gene copy number'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The rejected claims are drawn to methods for screening for a cancer comprising determining SPHK1 human gene copy number, and as such encompass determining the copy number of any 'sphingosine kinase 1 (SPHK1) human gene'.

The nature of the claims requires knowledge of a correlation between copy number of the broadly claimed 'sphingosine kinase 1 (SPHK1) human gene' and the suggestion of the presence of a precancerous lesion or a cancer.

Direction provided by the specification and working example

The specification of the instant application asserts that it has been determined that SPHK1 is amplified and/or overexpressed in human cancers (p.66). The specification asserts that human chromosome region 17q25 is one of the most frequently amplified regions in human cancer, and that in the process of characterizing a 17q25.2 amplicon SPHK1 was found amplified in several tumor samples (p.67). The specification teaches that amplification of SPHK1 was determined by microarray

analysis (p.67).

The specification teaches several definitions relevant to the breadth of the rejected claims. The specification teaches that 'cancer' includes the presence of cells possessing characteristics typical of cancer-causing cells, and specifically includes leukemic cells. The specification further defines a 'gene' as a region on genome capable of being transcribed to an RNA that has a regulatory or catalytic function or encodes a protein and encompasses spice variants, allelic variants, and transcripts arising from alternative promoter or poly-adenylation sites (p.32). The specification further defines SPHK1 as encompassing polymorphic variants, alleles, mutants, and interspecies homologs with various, not clearly defined, levels of homology and identity to GenBank NM_021972 (nucleic acid sequence), Genbank NP_069907.2 (polypeptide sequence), and SEQ ID NO: 1, 2, and 3 (nucleic acid and polypeptide sequences). (p.66).

Because the claimed method comprises determining gene amplification, it is relevant to point out that the instant specification broadly defines the term 'amplification' as encompassing amplification, duplication, and multiplication, of a gene yielding about 3.0 fold or more copies. However, an SPHK1 gene copy number of less than 3.0 fold can still be considered an amplification (p.34). The specification further defines an 'amplicon' as the amplification product of a gene, indicating that the term includes partially amplified SPHK1 (p.35).

Thus given the definitions provided by the specification, the claimed methods encompass detecting amplification of any portion of a gene sequence with even a small

degree of sequence similarity to the any variant of an SPHK1 gene or cDNA sequence (where it is noted that the provided SEQ ID NO: 1 and 2 are cDNA sequences, and not genomic sequences that encode the SPHK1 transcript). For example, a polymorphic variant of an SPHK1 gene which contains a three nucleotide repeat insertion would be a gene amplification.

The specification provides an example of the analysis of SPHK1 gene amplification in cells from human tumors (Examples I, II, and III, pages 111-114). The Examples of the specification teach that DNA microarray based CGH was used to survey the genome for gene amplification, and it was determined that SPHK1 is frequently amplified in tumor tissues and cell lines. The specification teaches analysis of SPHK1 gene copy number in breast, ovarian, colon, bladder, and lung tumors (Table 1). The specification teaches that SPHK1 gene amplification was detected from 3% to 33% of the time. For example, amplification was detected in 1 out of 30 lung tumor samples. In the case of bladder cancer, amplification was found in 3 out of 9 samples (33%).

The specification does not provide the sequence of the microarray probes used to determined SPHK1 gene amplification, nor the method in which gene amplification was determined for the data in Table 1, nor the nature of the amplicon (e.g. the portion of the SPHK1 gene that is amplified in a tumor sample).

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection and quantitation of a particular nucleic acid sequence in a sample is high, the level of

unpredictability in associating any particular gene or copy number of a gene with a phenotype is even higher, where in the instant case the unpredictability is intensified by the breadth of the claims with regard to the SPHK1 gene and control copy number from any 'corresponding tissue'. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Though the prior art teaches a role of sphingosine kinase in the development of cancer phenotypes (Xia et al, 2000, as cited in the IDS), the prior art does not teach the reliable association of amplification of any SPHK1 gene as broadly claimed and defined in the instant specification with the suggestion of cancer.

And while the specification teaches the breadth of the term 'SPHK1 gene', the examples presented in the specification do not address the different sequences encompassed by the claims. For example while the claims encompass analysis of any polymorphic variant, the specification does not teach the analysis of any variants of the SPHK1 gene. The art teaches a variety of polymorphisms in the SPHK1 gene including at least 27 SNPs (GeneCard for protein-coding SPHK1, pages 7-8). Notably, one SNP (rs3744040; CAG to TAG) creates a Gln to STOP codon change in the protein-coding region. Based on the prior art of Xia et al (which teaches a role of over expression of the sphingosine kinase in cancer development) coupled with the teachings of the instant application (which asserts that gene amplification leads to overexpression (Table 2)), it is unpredictable as to whether or not amplification of a gene containing, for example, the rs3744040 SNP (coding for a truncated amino acid sequence), or any other SNP, would be indicative of cancer.

Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). It is thus not established by the teachings provided in the instant specification whether or not a measure of copy number of any SPHK1 gene, as broadly defined in the specification, can reliably suggest the presence of cancer.

Quantity of experimentation required

A large amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include examining any possible variant of the SPHK1 gene as broadly defined in the specification to determine which of the possible myriad of sequences are suitable for screening for the cancers recited in the claims. Application of the method to the specifically recited forms of cancer would require validation every possible gene variant to establish that such 'SPHK1 human gene' copy number suggests the presence of cancer'. Such experimentation would involve the analysis of an enormous number of nucleic acid sequences.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ as lacking enablement. Applicants' arguments have been fully considered but are not found to be sufficient to put the claims in condition for allowance.

Applicants argue (p.6-7 of Remarks) that the construction of claims must be guided by what would be considered reasonable by one of ordinary skill in the art, and that the Examiner has not explained why the ordinary artisan would consider it reasonable to construe the recited SPHK1 gene, naturally present in human tissues, to encompass such a wide variety of nucleic acid sequences that the claims lack written description and enablement. The argument has been considered but is not found to be persuasive. The Examiner reiterates that MPEP 2111 addresses proper claim interpretation, specifying:

> The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).

In the instant case of the rejected claims, the Examiner must consider the very broad definition of SPHK1 as provided by the Applicants' themselves in constructing the breadth of the claimed methods. The examiner maintains that the term SPHK1 encompasses a wide variety of nucleic acid sequences, as specifically contemplated by the definition of the Applicants (p.66 of the specification), where the breadth of nucleic acids encompassed by the methods is not enabled by the particular examples and teachings of the specification in combination with the knowledge of the skilled artisan. In this case, as explained in the rejection, it is the specific teachings of the disclosure with regard to what Applicants consider to be encompassed by the SPHK1 gene that would make the ordinary artisan consider it reasonable to construe the recited SPHK1, in the absence of any structural limitations, to encompass a wide variety of nucleic acid sequences. The Examiner maintains the claims are properly rejected for lack of enablement when given their broadest reasonable interpretation in light of the teachings of the specification.

The rejection is **MAINTAINED.**

Maintained Claim Rejections - 35 USC § 112 1st – Written Description

3. Claims 1, 2, and 135-138, 145, and 147-151 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is referred to the guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing cancer comprising determining SPHK1 human gene copy number. The rejected claims provide no structural limitation regarding what is encompassed by the term 'sphingosine kinase 1 (SPHK1) human gene'.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to screening for cancer by determining SPHK1 human gene copy number in a test sample. The specification teaches a broad definition of 'gene' as a region on the genome that is capable of being transcribed to an RNA (p.32), and encompasses all SPHK1 transcripts that may be found including splice variants, allelic variants, and transcripts that occur because of alternative promoter sites or alternative poly-adenylation sites (p.33). The specification further teaches a broad definition of 'SPHK1', indicating that the term 'SPHK1' may include polymorphic variants, alleles, mutants, and interspecies homologs that have (i) for example as little as 60% nucleotide identity to GenBank NM_021972, (ii) as little as 65% amino acid homology to GenBank NP_068807.2, (iii) for example as little as 60% homology with the nucleotide sequence of SEQ ID NO: 1, or (iv) 'substantial sequence homology with the encoded amino acid (for example, SEQ ID NO: 2)' with no clear definition of 'substantial sequence homology' (p.66). Additionally, the specification teaches a definition of 'amplicon' as an amplification product that may include a part of SPHK1 (p.35). Thus the rejected claims encompass analysis of any portion of any

variant of any SPHK1 human gene, which may include gene sequences very different from the disclosed SEQ ID NO: 1, and genes that encode polypeptides very different from the disclosed SEQ ID NO: 2, including sequences containing any polymorphisms (e.g. any insertion, deletion, or repeat at any location within the gene) and mutations not taught by the instant specification and not yet known in the art.

In analyzing whether the written description requirement is met for genus claims for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Nucleic acids of such a large genus as encompassed by the rejected claims have not been taught by the specification. The specification of the instant application discloses only SEQ ID NO: 1 (a human SPHK1 cDNA sequence), SEQ ID NO: 3 (the protein coding portion of SEQ ID NO: 1), and SEQ ID NO: 2 (the amino acid sequence encoded by SEQ ID NO: 3).

In analyzing whether the written description requirement is met for genus claims it is next determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the sequence of the human SPHK1 gene (SEQ ID NO: 1 and 3) and the encoded amino acid sequence (SEQ ID NO: 2). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or

variants of the disclosed sequence that would allow for the diagnosis of cancer based on amplification of the non-disclosed gene.

> Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:
>
> > It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, with the exception of a method for diagnosing cancer comprising determining the copy number of a gene consisting of the particular sequences disclosed in the specification, one of skill in the art cannot envision the detailed chemical structure of the encompassed polynucleotides (i.e. any SPHK1 genes the amplification of which is suggestive of cancer), regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that any genetic variants or fragment of the gene is part of the claimed invention and a qualitative description of the nature of the variant (e.g. amplification is associated with cancer).

In conclusion, the limited information provided regarding the association of SPHK1 (including disclosure only of SEQ ID NO: 1, 2, and 3) gene amplification with cancer is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of methods comprising the analysis of any gene variants or fragments besides those particularly disclosed in the specification at the time the

application was filed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st¶ as lacking adequate written description of the claimed subject matter. Applicants' arguments (p.6-7 of Remarks) regarding the rejection of claims under 35 USC 112 1st ¶ have been addressed in the previous Response to Remarks in this Office Action. The Examiner maintains that the specific teachings of the disclosure with regard to what Applicants consider to be encompassed by the SPHK1 gene would make the ordinary artisan consider it reasonable to construe the recited SPHK1, in the absence of any structural limitations, to encompass a wide variety of nucleic acid sequences, where such a wide variety with the functionality of being indicative of cancer, is not described by the instant specification.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections – 35 USC § 102

4. The rejection of claims 1 and 2 under 35 USC 102 as anticipated by Michelland et al (1999), as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendment to independent claim 1 such that the claim no longer encompasses lung cancer.

New Claim Rejections - 35 USC § 102

5. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Roylance et al (1999).

Roylance et al teaches the comparative genomic hybridization analysis of breast cancer tumor cells as compared to non-cancerous reference tissue.

Regarding claim 1, the reference teaches CGH analysis of DNA extracted from breast tumors (p.1433 – CGH). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (Fig 1 and 2, p.1435, left col. lns.10-11), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in multiple tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.1433 - CGH), relevant to part (a) of claim 1. Relevant to part (b) of claim 1, the reference also teaches (p.1433 – CGH) that the CGH analysis included the simultaneous analysis of labeled normal reference DNA by hybridization to normal metaphase spreads. Because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis of results is a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human breast tissue has two copies of the SPHK1 gene).

Regarding claim 2, the reference teaches the use of normal DNA as a control, and hybridization to normal metaphase spreads (p.51 – CGH). Thus the comparison to the control is a comparison to a normal diploid sample in which the copy number of the 17q region is two copies per cell.

6. Claims 145 and 147 are rejected under 35 U.S.C. 102(b) as being anticipated by Michelland et al (1999).

Michelland et al teaches the comparative genomic hybridization analysis of lung cancer cells as compared to non-cancerous tissue.

Regarding claim 1, the reference teaches CGH analysis of DNA extracted from lung tumors (p.22 – Tumor samples; p.23 – DNA extraction, labeling and in situ hybridization; Digital analysis). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (p.23 – High-grade NE lung tumors, NSCLC; Tables 1, 3, and 4), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in at least 9 tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.23 – Digital image analysis), relevant to part (a) of claim 1. Further relevant to part (a) of claim 1, the analysis of the 17q region by CGH utilizes nick translated DNA, which comprises 'an SPHK1-specific probe' as recited in the claim. Relevant to part (b) of claim 1, the reference also teaches (p.23 – DNA extraction, labeling and in situ hybridization, Digital image analysis) that the CGH analysis included

the simultaneous analysis of labeled DNA from tumor and normal tissue by hybridization to normal metaphase spreads. Because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis results in a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human lung tissue has two copies of the SPHK1 gene). The reference further teaches that amplification of the 17q region (which contains the SPHK1 gene) is a chromosomal amplification that suggests the presence of cancer (e.g. Table 3 and p.28, right col, last paragraph).

Regarding claim 147, the reference teaches the use of normal DNA as a control, and hybridization to normal metaphase spreads (p.51 – CGH). Thus the comparison to the control is a comparison to a normal diploid sample in which the copy number of the 17q region is two copies per cell.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the teachings of Michelland et al as set forth in the previous Office Action. While the rejection as particularly set forth in the previous Office Action is withdrawn in light of the amendments to the claims, the teachings of the same reference have been applied to the newly presented claims, and thus a response to Applicants traversal is appropriate. Applicants argue (p.7 of Remarks) that Michelland et al dopes not teach or suggest use of an SPHK1-specific probe. The argument is not persuasive. The Examiner maintains that in the analysis of genetic content using CGH analysis of nick

translated DNA, the CGH probe comprises 'an SPHK1-specific probe'.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections - 35 USC § 103

7. The rejection of claims 135-138 under 35 USC 103 as obvious in view of the teachings of Michelland et al (1999) and the rejection of claims 139-144 under 35 USC 103 as obvious in view of the teachings of Michelland et al (1999) in view of Melendez et al (2000) are **WITHDRAWN** in light of the amendments to independent claims 1 and 139 such that the claims no longer encompass lung cancer.

New Claim Rejections - 35 USC § 103

8. Claims 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roylance et al (1999).

Roylance et al teaches the comparative genomic hybridization analysis of breast cancer tumor cells as compared to non-cancerous reference tissue. The reference teaches CGH analysis of DNA extracted from breast tumors (p.1433 – CGH). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (Fig 1 and 2, p.1435, left col. lns.10-11), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in multiple tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.1433 - CGH), relevant to

part (a) of claim 1. Relevant to part (b) of claim 1, the reference also teaches (p.1433 – CGH) that the CGH analysis included the simultaneous analysis of labeled normal reference DNA by hybridization to normal metaphase spreads. Because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis of results is a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human breast tissue has two copies of the SPHK1 gene).

Thus Roylance et al teaches all of the limitations of claim 1, from which claims 135-138 depend.

Roylance et al does not particularly teach detectable amplification of specifically at least three-fold, four-fold, five-fold, or ten-fold, as required by claims 135-138, respectively.

However, Roylance et al does teach, when comparing hybridization of a tumor DNA and normal control DNA with a metaphase chromosome spreads, that a chromosome region was considered gained if the ratio of tumor to normal DNA was >1.15:1 (p.1433 - CGH). Thus based on the express teachings of detection of locus amplification, modification of the methods specifically taught in Roylance et al as required by the rejected claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because Roylance et al provides teachings as to the amplification of the chromosome 17q, including the portion of 17q that comprises the SPHK1 gene, in the development of breast cancer, it would be

obvious for the skilled artisan to consider any amplification of the 17q region, including amplifications of at least three-fold, four-fold, five-fold, or ten-fold as, as required by the claims where each claimed fold amplification is encompassed amplification ratios that exceed the ratio as taught by Roylance et al, as suggestive of the presence of breast cancer. One would have been motivated to include higher levels of 17q amplification as a determinant of the presence of breast cancer based on the teachings of Roylance et al that amplification of 17q is indicative of cancer, thus providing a greater flexibility in application of the methods of Roylance et al in the analysis of breast cancer. The skilled artisan would have a reasonable expectation of success based on the express teachings Roylance et al that amplification of 17q is indicative of cancer.

9. Claims 139-144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roylance et al (1999), as applied to claims 135-138 above, in view of Meledez et al (2000) as evidenced by the provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.

The teachings of Roylance et al are applied to claims 139-144 as they were previously applied to claims 135-138.

Relevant to claims 139 and 140, Roylance et al teaches determining in a test sample SPHK1 gene copy number, and comparing the test gene copy number to data for a control gene copy number, wherein the control gene copy number is two copies per cell, wherein gene amplification is indicative of cancer.

Roylance et al does not specifically teach an SPHK1 gene that encodes an

mRNA comprising SEQ ID NO: 3 (as required by part (a) of claim 139), a control gene copy number obtained from a control sample of a same tissue type as the test sample, (as required by part (b) of claim 139), or detectable amplification of specifically at least three-fold, four-fold, five-fold, or ten-fold (as required by claims 141-144, respectively).

However, such additions to the methods of the express teachings of Roylance et al would have been obvious to one of ordinary skill in the art at the time the invention was made.

Regarding the limitations of part (a) of claim 139, Melendez et al teaches an analysis of the human SPHK1 gene indicating that it is located at chromosome locus 17q25.2 and encodes an mRNA comprising the sequence of SEQ ID NO: 3 (p.23 – huSPHK1 cDNA and peptide sequences, evolutionary comparison, genomic localization; Figure 1; and provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.). Thus it would have been obvious to the skilled artisan to perform the method of Ryolance et al for the analysis of the 17q locus comprising the SPHK1 gene encoding an mRNA comprising SEQ ID NO: 3, where the genomic location and sequence of the mRNA are specifically taught by Melendez et al. One would have been motivated to include the particularly required SPHK1 gene based on the teachings of Melendez et al concerning the genomic localization of the SPHK1 gene and the sequence of its encoded mRNA, and the teachings of Ryolance et al that the 17q locus is amplified in cancer.

Regarding the limitation of part (b) of claim 139 that the control gene copy number is obtained from a control sample of a same tissue type as the test sample, it

would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any known diploid tissue sample in a CGH study to provide a control gene copy number of two-copies per cell, including a control sample of the same tissue type. One would have been motivated to use the same tissue type in order to provide alternative techniques that would provide predictable results.

Regarding the limitations of claims 141-144, as discussed in the rejection above, Roylance et al teaches that when comparing hybridization of a control with a sample, a region was considered gained when the tumor DNA to normal DNA ratio was >1.15:1 (p.1433 - CGH). Thus based on the express teachings of detection of amplification, modification to the methods specifically taught in Roylance et al as required by claims 141-144 would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because Roylance et al provides teachings as to the amplification of the chromosome 17q, including the portion of 17q that comprises the SPHK1 gene, in the development of breast cancer, it would be obvious for the skilled artisan to consider any amplification of the 17q region, including amplifications of at least three-fold, four-fold, five-fold, or ten-fold as, as required by the claims where each claimed fold is suggestive of the presence of cancer. One would have been motivated to include higher levels of 17q amplification as a determinant of the presence of cancer based on the teachings of Roylance et al that amplification of 17q is indicative of the presence of breast cancer, thus providing a greater flexibility in application of the methods of Roylance et al in the detection of cancer. The skilled artisan would have a

reasonable expectation of success based on the express teachings Roylance et al that amplification of 17q is indicative of cancer.

10. Claims 148-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michelland et al (1999).

Michelland et al teaches CGH analysis of DNA extracted from lung tumors (p.22 – Tumor samples; p.23 – DNA extraction, labeling and in situ hybridization; Digital analysis). The reference specifically teaches the analysis of chromosomal gain at chromosome 17q (p.23 – High-grade NE lung tumors, NSCLC; Tables 1, 3, and 4), a region which encompasses the human SPHK1 gene (see for example Figure 1, which indicates gain of the region including SPHK1 gene in at least 9 tumor samples). Thus the analysis of tumor DNA by CGH is determining SPHK1 gene copy number in a sample from a region suspected to be cancerous and generating data for a test gene copy number (p.23 – Digital image analysis), relevant to part (a) of claim 1. Further relevant to part (a) of claim 1, the analysis of the 17q region by CGH utilizes nick translated DNA, which comprises 'an SPHK1-specific probe' as recited in the claim. Relevant to part (b) of claim 1, the reference also teaches (p.23 – DNA extraction, labeling and in situ hybridization, Digital image analysis) that the CGH analysis included the simultaneous analysis of labeled DNA from tumor and normal tissue by hybridization to normal metaphase spreads. Because a normal tissue has two copies of any given chromosomal locus (i.e. diploidy) the analysis results in a comparison of test and control gene copy numbers, where the control gene copy number is two, and such a control

gene copy number represents the SPHK1 human gene copy number of corresponding normal, cancer-free human lung tissue (i.e. normal cancer-free human lung tissue has two copies of the SPHK1 gene). The reference further teaches that amplification of the 17q region (which contains the SPHK1 gene) is a chromosomal amplification that suggests the presence of cancer (e.g. Table 3 and p.28, right col, last paragraph). Thus Michelland et al teaches all of the limitations of claim 145, from which claims 148-151 depend.

Michelland et al does not particularly teach detectable amplification of specifically at least three-fold, four-fold, five-fold, or ten-fold, as required by claims 148-151, respectively.

However, Micehlland et al does teach, when comparing hybridization of a control with a sample, that over-representation was indicative of a high-level amplification (amplification site) when the ratio exceeded 2.0' (p.23, right col., lns.12-19). Thus based on the express teachings of detection of amplification in excess of two-fold amplification (i.e. a ratio that exceeds 2.0), modification to the methods specifically taught in Michelland et al as required by the rejected claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because Michelland et al provides teachings as to the amplification of the chromosome 17q, including the portion of 17q that comprises the SPHK1 gene, in the development of lung cancer (as provided in Figure 1), it would be obvious for the skilled artisan to consider any amplification of the 17q region, including amplifications of at least three-fold, four-fold, five-fold, or ten-fold as, as required by the claims where each claimed

fold amplification is encompassed by the amplification ratio that exceeds 2.0 as taught by Michelland, as suggestive of the presence of cancer. One would have been motivated to include higher levels of 17q amplification as a determinant of the presence of cancer based on the teachings of Michelland et al that amplification of 17q, including high-level amplification, is indicative of cancer, thus providing a greater flexibility in application of the methods of Michelland et al in the detection of cancer. The skilled artisan would have a reasonable expectation of success based on the express teachings Michelland et al that amplification of 17q is indicative of cancer.

11. Claim 146 is rejected under 35 U.S.C. 103(a) as being unpatentable over Michelland et al (1999), as applied to claims 135-138 above, in view of Meledez et al (2000) as evidenced by the provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.

The teachings of Michelland et al are applied to claims 146 as they were previously applied to claims 148-151.

Michelland et al teaches determining in a test sample SPHK1 gene copy number, and comparing the test gene copy number to data for a control gene copy number, wherein the control gene copy number is two copies per cell, wherein gene amplification is indicative of cancer.

Michelland et al does not specifically teach an SPHK1 gene that encodes an mRNA comprising SEQ ID NO: 3 (as required by part (a) of claim 139).

However, such additions to the methods of the express teachings of Michelland et al would have been obvious to one of ordinary skill in the art at the time the invention was made.

Regarding the limitations of claim 146, Melendez et al teaches an analysis of the human SPHK1 gene indicating that it is located at chromosome locus 17q25.2 and encodes an mRNA comprising the sequence of SEQ ID NO: 3 (p.23 – huSPHK1 cDNA and peptide sequences, evolutionary comparison, genomic localization; Figure 1; and provided Blast 2 Sequences results – SEQ ID NO: 3 – Melendez et al.). Thus it would have been obvious to the skilled artisan to perform the method of Michelland et al for the analysis of the 17q locus comprising the SPHK1 gene encoding an mRNA comprising SEQ ID NO: 3, where the genomic location and sequence of the mRNA are specifically taught by Melendez et al. One would have been motivated to include the particularly required SPHK1 gene based on the teachings of Melendez et al concerning the genomic localization of the SPHK1 gene and the sequence of its encoded mRNA, and the teachings of Michelland et al that the 17q locus is amplified in cancer.

Conclusion

12. No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634

/Jehanne S Sitton/
Primary Examiner, Art Unit 1634